

# Clinical Features of Bone Complications and Prognostic Value of Bone Lesions Detected by X-ray Skeletal Survey in Previously Untreated Patients with Multiple Myeloma

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**Abstract** Multiple myeloma is usually associated with the presence of lytic bone lesions. We reviewed the clinical and laboratory features of patients with newly diagnosed myeloma bone disease and evaluated the prognostic significance of different X-ray image patterns in symptomatic MM patients. We retrospectively reviewed 260 patients with newly diagnosed MM. X-ray image patterns of patients were correlated with hematologic parameters, therapeutic reaction and patient survival. Patients with the X-ray imaging pattern of grade 2–4 had significantly higher marrow plasma cells levels, marrow CD138<sup>+</sup> D38<sup>+</sup> cell percentage, ECOG performance score, and serum IL-6 level than grade 0–1. Univariate analysis demonstrated that skeletal lytic changes associated with rapid progression. There is a high incidence of myeloma bone disease (MBD) in patients of MM in China. Patients of extensive bone lesions have more severe alterations in hematologic parameters than do those without bone lesions and severe bone lesions is an important adverse prognostic factor associated with a short TTP.

**Keywords** Multiple myeloma · Myeloma bone disease · Bone lesions · Prognosis

## Introduction

Multiple myeloma (MM) is a malignant disorder of plasma cells that affects the bone marrow and is associated with MBD including bone pain, lytic bone lesions, pathologic fractures, and hypercalcemia. MM bone lesions result not only from the direct sediment of multiple myeloma cells within the bone, but also from the release of soluble factors by both the tumor and the bone microenvironment which result in stimulation of osteoclast activity and bone resorption.

Conventional radiographs of the skeleton are routinely obtained after diagnosis of patients with myeloma. Abnormal skeletal radiographs are detected in more than 80% of patients. The skeletal X-ray changes in multiple myeloma range from apparently normal bones to extensive bone lesions with concomitant pathological fractures [1]. Durie and Salmon found that the extent of bone lesions correlated strongly with tumor load and prognosis and therefore radiograph changes was included in their clinical staging system. The presence of rounded, punched-out lytic bone lesions indicates stage III disease [2]. However, the prognostic value of radiographic findings may be controversial, some studies have found X-ray changes not to be a reliable predictor of survival in myeloma since in some series patients with skeletal surveys that appeared normal actually had a worse prognosis [3, 4].

In our present study, we reviewed the clinical and laboratory features of patients with newly diagnosed MM and evaluated the correlation of different X-ray image patterns with hematologic parameters, therapeutic response and patient survival.

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## Patients and Methods

### Patients and Diagnosis

Two hundred and sixty previously untreated patients with MM were reviewed in the Blood Disease Hospital of Chinese Academy of Medical Science in Tianjin, from February 1995 to May 2008 and the median follow-up for all patients was 25 months (1–145 months). Diagnosis was confirmed in all cases by immuno-fixation electrophoresis (IFE), bone marrow biopsy, serum and urine protein electrophoreses and quantitation of serum immuno-globulin levels. These lab works were performed before initiation of antimyeloma therapy. Patients were staged according to criteria defined by Durie and Salmon [2] and International Staging System (ISS) [5] for MM as well.

### MBD Evaluation

All patients underwent modified skeletal survey including X-ray of skull, limb bone, ribs, dorsolumbar spine and pelvis within 1 week after diagnosis and radiographic studies were obtained before the start of treatment. X-ray image patterns were defined as described previously [4]. Briefly, according to X-ray evaluation of the patients, bone involvement was graded to five groups: normal (grade 0); diffuse osteoporosis (grade 1); minimal lytic changes (lytic changes in one of the skeletal survey locations as above, grade 2); extensive lytic changes without pathologic fractures (lytic changes in more than one of the skeletal survey locations as statement, grade 3); minimal or extensive lytic changes but with pathologic fractures (grade 4). Pain scores were calculated by multiplying the score for pain severity (graded from 0 to 3) by the score for pain frequency (graded from 0 to 3). A pain score of 0 indicates no pain, and a pain score of 9 indicates constant, severe pain [6]. The occurrence of any hypercalcemia or hypocalcemia (as defined by the presence of symptoms or a serum calcium concentration, adjusted for the serum albumin concentration, of more than 2.75 mmol/l or less than 2.15 mmol/l) was also noted.

### Other Laboratory Data

Studies performed in the clinical laboratory included a complete blood count; serum-chemistry tests; 24-h urinary protein excretion; serum beta-2-microglobulin (B2 M); serum Interleukin-6 (IL-6); C-reactive protein (CRP) levels; bone marrow cellularity, percentage of plasma cells; bone marrow flow cytometer detection, percentage of CD138<sup>+</sup> CD38<sup>+</sup> cells and conventional karyotyping. These tests were performed at baseline before protocol therapy.

### Initial Treatment and Assessment of Response

Induction chemotherapy regimens included (a) vincristine, doxorubicin or liposomal doxorubicin and dexamethasone (VAD) [7, 8]; (b) melphalan and dexamethasone with or without thalidomide (MP/MPT); (c) vincristine, carmustine, melphalan, cyclophosphamide, and prednisone (M2); (d) chemotherapy including bortezomib. Response to treatment was assessed according to the EBMT criteria [9].

### Follow-up and Outcome

Overall survival (OS) was calculated from the date of diagnosis to death from any cause or to the last follow-up visit. Time to progression (TTP) was defined from the start of treatment until the increase or re-appearance of a monoclonal protein in serum/urine or the last follow-up visit, whichever occurred first.

### Statistical Analysis

Hematologic parameters were compared between subgroups of patients determined on the basis of their skeletal imaging appearance by using the non-parametric Mann–Whitney test for the numeric variables and the chi-squared test for the categoric variables. The Kaplan–Meier method was used to estimate OS and TTP, with group comparisons made using the log-rank test. The Cox proportional hazards model was applied to all variables that had shown statistical significance at the univariate analysis. *P*-values < 0.05 were considered to be statistically significant.

## Results

### Patients and Disease Features

Characteristics of patients in this study are shown in Table 1. Majority of the patients (75.7%) had bone pain at presentation. Two hundred and thirty-two patients performed serum calcium at baseline before protocol therapy, 56 (24.0%) with hypocalcemia, 131 (56.5%) with normal level and 45 (19.5%) with hypercalcemia.

### X-Ray Image Findings

In this group of 260 patients with MM, there were 27 (10.3%) of grade 0, 20 (7.7%) of grade 1, 34 (13.0%) of grade 2, 86 (33.2%) of grade 3 and 93 (35.8%) of grade 4. According to radiographic data, skull (66.7%) was most frequently involved in lytic lesions, followed by ribs

**Table 1** Characteristics of patients

Features	Percentage
Male	65.5
Age > 60 years	38.7
Myeloma type	
IgG	42.5
IgA	24.3
Light chain	24.0
Others <sup>a</sup>	9.2
ISS	
I	17.2
II	47.5
III	35.3
DS	
Ia	2.4
IIa	6.9
IIb	3.0
IIIa	70.7
IIIb	17.0
Painful area	
Low back	60.7
Sternocostal part	54.7
Limbs	7.3
Pelvis	4.7
Whole body	5.3
Pain score	
0	27.3
1–3	8.1
4–6	33.2
7–9	31.4
Calcium	
Hypocalcemia < 2.15 mmol/l	24.0
Normal	56.5
Hypercalcemia ≥ 2.75 mmol/l	19.5

<sup>a</sup> “Others” include myelomas of the IgD subtype, nonsecretory tumors, and myelomas of unknown subtypes

(47.5%) and dorsolumbar spine (65.8%) was most frequently involved in pathologic or compression fractures followed by ribs (51.3%) too (Table 2).

#### X-Ray Image Findings Correlation with Hematologic Parameters

Patients with the X-ray image pattern of grade 4 had significantly higher levels of marrow plasmacytosis ( $P = 0.040$ ) and higher ECOG performance score ( $P < 0.001$ ) than did other groups (Table 3). Moreover, comparison of grade 4 with grade 0–1 showed that the former group had higher level of serum IL-6 than the latter two groups ( $P < 0.05$ ). In contrast to patients without bone lesions (grade 0–1), patients of grade 2–4 had elevated marrow CD138<sup>+</sup> CD38<sup>+</sup> cell percentage ( $P < 0.001$ ). However, patients of grade 4 presented with hypocalcemia ( $P < 0.05$ ) more often than other groups. There were no significant differences in patients’ age, hemoglobin, chromosome karyotype, B2 M, CRP, serum creatinine, serum LDH, serum phosphorus, and serum albumin among the five X-ray image patterns (Table 3).

#### X-Ray Image Findings Correlation with Response to Treatment

Response to initial induction chemotherapy (3–4 cycles of treatment), which was assessed for 230 patients according to the EBMT criteria [9], showed complete response (CR) in 30 (13.0%), near complete response (nCR) in 45 (19.6%), very good partial response (VGPR) in 35 (15.2%), and partial response (PR) in 94 (40.9%). Response (CR + nCR + VGPR + PR) quality did not differ significantly in the five groups of patients ( $P = 0.588$ ).

#### X-Ray Image Findings Correlation with Survival and Disease Progression

Patients were regularly followed up in our hematology department or by telephone. The median OS was 38 months (range 1–145 months) and median TTP was 25 months (range 0.5–93 months). One hundred and forty-two patients had died by the time of completion of this study.

Median OS of grade 0–1 patients was 36 months while median OS of grade 2–4 patients was 39 months. Comparison of overall survival did not show a trend for decreasing

**Table 2** X-ray image findings

Lesion site	Osteoporosis (%)	Lytic lesions (%)	Pathologic or compression fractures (%)
Skull	77 (49.4)	137 (66.7)	0
Ribs	115 (73.7)	82 (40.1)	49 (51.3)
Pelvis	77 (49.4)	80 (38.9)	0
Limb bone	70 (44.9)	97 (47.5)	5 (5.3)
Dorsolumbar spine	102 (65.4)	41 (19.8)	63 (65.8)
No. of patients	156	205	96

**Table 3** Comparison of hematologic parameters according to X-ray imaging patterns

Variable	X-ray			P-value		
	Grade 0–1 (n = 47)	Grade 2–3 (n = 120)	Grade 4 (n = 93)	Grade 0–1 vs. Grade 2–3	Grade 2–3 vs. Grade 4	Grade 0–1 vs. Grade 4
Age > 60 years <sup>a</sup>	19 (40.4%)	47 (39.2%)	50 (53.8%)	0.235	0.420	0.605
ECOG score ≥ 3 <sup>a</sup>	15 (31.9%)	27 (22.5%)	56 (60.2%)	0.911	<0.001	0.005
Abnormal chromosome karyotype <sup>a</sup>	8 (17.0%)	19 (15.8%)	29 (31.2%)	0.688	0.111	0.111
B2 M > 5.5 mg/l <sup>a</sup>	15 (31.9%)	34 (28.3%)	45 (48.4%)	0.686	0.684	0.491
Hypercalcemia <sup>a</sup>	6 (12.8%)	23 (19.2%)	16 (17.2%)	0.226	0.358	0.590
Hypocalcemia <sup>a</sup>	10 (21.3%)	17 (14.2%)	29 (31.2%)	0.296	0.038	0.05
Hb (g/l) <sup>b</sup>	72.8 ± 3.8	77.7 ± 2.5	83.2 ± 2.8	0.663	0.754	0.462
CRP (mg/l) <sup>b</sup>	14.4 ± 3.8	15.2 ± 2.7	13.4 ± 2.5	0.141	0.448	0.295
Creatinine (μmol/l) <sup>b</sup>	131.5 ± 16.8	124.7 ± 13.5	139.3 ± 17.9	0.505	0.451	0.827
Marrow plasma cytosis (%) <sup>b</sup>	33.8 ± 3.9	33.3 ± 2.9	41.6 ± 2.5	0.225	0.040	0.045
Marrow CD138 <sup>+</sup> CD38 <sup>+</sup> cell (%) <sup>b</sup>	5.6 ± 0.7	15.4 ± 2.8	27.4 ± 4.7	0.002	0.001	<0.001
Serum IL-6 (pg/ml) <sup>b</sup>	93.8 ± 5.6	106.8 ± 5.1	135.4 ± 5.9	0.390	0.175	0.045
Serum phosphorus (mmol/l) <sup>b</sup>	1.7 ± 0.2	1.6 ± 0.1	1.8 ± 1.5	0.601	0.930	0.600
Serum LDH (U/l) <sup>b</sup>	213.3 ± 24.8	212.3 ± 25.6	205.4 ± 20.7	0.129	0.830	0.150
Serum albumin (g/l) <sup>b</sup>	34.7 ± 1.5	34.5 ± 0.2	33.8 ± 0.5	0.205	0.970	0.191

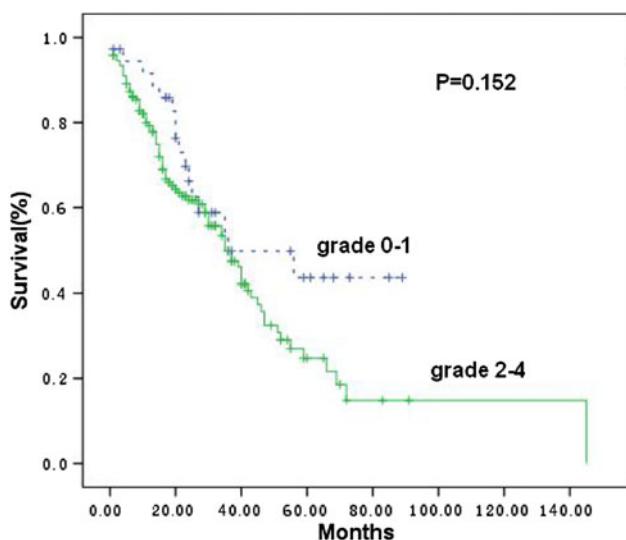
<sup>a</sup> Data are the number of patients and percentage

<sup>b</sup> Data are the mean ± SD

survival ( $P = 0.152$ ) with skeletal lytic changes. Examination of the survival curves demonstrated that patients with normal or osteoporotic bones survived less well than anticipated (Fig. 1).

Univariate analysis demonstrated that skeletal lytic changes ( $P = 0.034$ ), CRP ( $P = 0.015$ ), hemoglobin ( $P = 0.015$ ), marrow CD138<sup>+</sup> CD38<sup>+</sup> cell percentage ( $P = 0.010$ ) and myeloma type ( $P = 0.023$ ) had a profound impact on disease progression. The median TTP exceeded

28 months in patients without bone lesions (grade 0–1) but was only 20 months in patients with bone lesions (grade 2–4) (Fig. 2). However, at the multivariate analysis, performed with the five parameters that had shown significant prognostic value at the univariate analysis, the Cox proportional hazards model identified myeloma type, hemoglobin and CRP as the best significant and independent prognostic factors (Table 4). Skeletal lytic changes did not enter this model.

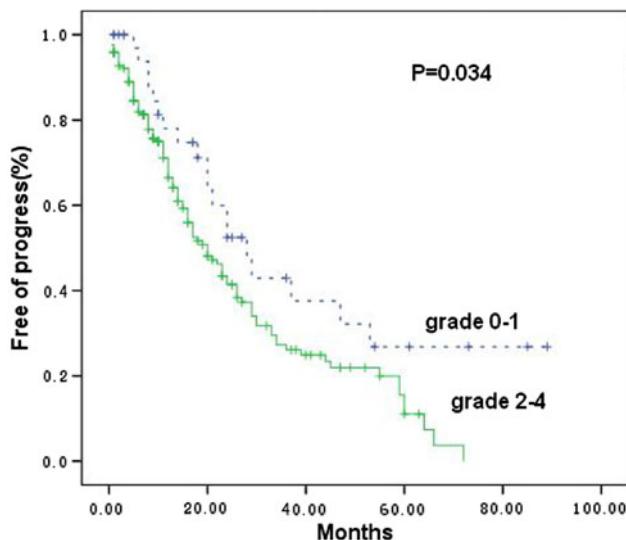


**Fig. 1** Survival of patients according to the presence or absence of skeletal lytic changes

## Discussion

Bone disease is a major feature of multiple myeloma. Myeloma-induced bone complications results from increased activity of osteoclasts, which are not accompanied by a proportional increase of osteoblast function. Our data showed that in this group of 260 patients with MM, 75.7% had bone pain, among which 31.4% had severe bone pain (pain scored 7–9); 82.0% patients had bone lesions to some extent. This was consistent to our previous result [10]. Therefore, MBD is a common and severe complication of MM patients in China.

X-ray image patterns of skeleton in MM patients had clinical and prognostic value. Our results showed that patients with extensive bone lesions at X-ray image, especially those with pathologic fractures, had several clinical parameters which indicated more severe disease. Firstly, serum IL-6 was high in patients with extensive bone lesions.



**Fig. 2** Time to progression of patients according to the presence or absence of skeletal lytic changes

**Table 4** Correlates of disease progression: multivariate analysis results with the Cox proportional hazards model

Variable	SE	Wald	Sig	RR
X-ray patterns	0.051	0.049	0.825	0.895
CRP	0.013	5.843	0.016	0.969
Hb	0.010	9.910	0.002	0.969
Marrow CD138 <sup>+</sup> CD38 <sup>+</sup> cell (%)	0.009	0.009	0.923	1.001
Myeloma type	0.600	1.007	0.001	0.123

IL-6, produced mainly by marrow stromal cells, is a growth factor for both osteoclasts and myeloma cells, stimulating them to proliferate and preventing them from apoptosis. IL-6 increases the pool of the early osteoclast precursors which then differentiate into mature osteoclasts [11]. Recently, Aikaterini et al. reported that IL-6 serum level in MM correlated well with bone turnover rate and might be useful in bone disease evaluation [12]. Secondly, the patients with lytic changes were associated with features of more advanced disease such as extensive marrow plasma cells and elevated marrow CD138<sup>+</sup> CD38<sup>+</sup> cell percentage [13, 14]. RANKL (receptor activator of NF- $\kappa$ B Ligand) is highly expressed by CD138<sup>+</sup> CD38<sup>+</sup> myeloma cells and its receptor RANK is expressed by osteoclast precursors and mature osteoclasts. The binding of RANKL on RANK promotes osteoclast maturation and activation which manifests as MBD aggravation [15]. Moreover, myeloma cells decrease OPG availability by internalizing it through CD138 molecular (syndecan-1) and degrading it within their lysosomal compartment [16]. Thus, in MM, the regulation of OPG decreases its availability in the marrow microenvironment, leading to inhibition of RANKL and increase of

osteoclast activation. Thirdly, the patients with extensive bone lesions were more frequently associated with high ECOG score which means MBD is the principal cause of poor quality of life of MM patients in China and these patients need effective treatment to ameliorate their quality of life. Lastly, the consistent ones with our previous finding but contrary to some other reports [13, 14], a high incidence of hypocalcemia were observed in MM patients, especially in those with pathologic fractures [10]. This discrepancy might be due to racial difference or the small number of patients included in our series. Therefore, hypocalcemia should be paid more attention to and given reasonable treatment and periodical monitoring by clinical doctors.

Among different X-ray image patterns, the response to initial induction chemotherapy had no evident discrepancy, which was also shown by previous study [14] and further studies in patients undergoing high-dose chemotherapy are needed.

We emphasize that bone lesions indicate a shorter TTP and this phenomenon may due to the more advanced disease and higher tumor burden. Our previous research has found that lytic bone lesion is associated with shorter TTP [17]. Although in this study, multivariable COX analysis did not show that bone lesions was an independent poor prognostic factor for TTP, more studies were needed to evaluate the relationship between bone lesions and disease progression. Comparison of survival curves, according to the grade of bone X-ray image changes, showed no significant difference: the grade of bone lesions at diagnosis did not seem to influence OS considerably. This finding has been reported in the literature [18] and, to some extent, indicates that our study population yielded valid results. Being convenient, fast and relatively inexpensive, conventional radiography is useful in the initial diagnostic work-up of patients with myeloma.

Compared with conventional radiography, positron emission tomography (PET)/computerized tomography (CT) scanning or magnetic resonance imaging (MRI) is sensitive for detecting occult bone disease. Therefore, once conventional radiography is inconclusive or negative in the setting of high clinical suspicion for bone disease, PET/CT or MRI may be useful [19]. Moreover, recent advances in genomics and proteomics have advanced our understanding of MBD pathogenesis, recognized novel mediators of disease process, and identified new therapeutic targets.

In conclusion, high incidence of MBD happens in MM of Chinese patients. Patients with extensive bone lesions at X-ray image especially those with pathologic fractures have more severe alterations in hematologic parameters than those without bone lesions. The presence of sever bone lesions is an important adverse prognostic factor associated with a short TTP. However, X-ray image patterns are not associated with response to initial induction chemotherapy and overall survival.

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